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Review Article

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The Progress of Chemical Constituents and Biological Activities of Grape Seeds

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Abstract

Grape seed is the key by-product after making the grape wine, and it always was produced food for livestock. However, there are many chemical constituents in grape seed, and which are good for human health. Some compounds together with their biological activities have been reported. In this minireview, we mainly described the recent progress of the chemical constituents and the biological activities of grape seed, to provide the reference for deeply exploring this by-product.

Keywords: Grape Seed, Chemical Components, Biological Activities

Introduction

Grape is one of the largest scaled plantings, and one of the most popular fruits in the world. According to the statistics from the International Organization of Vine and Wine, in 2019, the world's vineyard planted area was 7.34 million hm2. The total grape planting area of Spain, France and China ranks the top three in the world, which are 960,000 hm2, 790,000 hm2 and 780,000 hm2 respectively. Nowadays, wine has become synonymous with fashion and health, more and more people begin to drink wine at leisure. The statistics from the international organization for grape and wine showed that the world wine production is 25.7 billion litres in 2009, and the consumption is 23.7 billion litres. The by-product of wine production is grape pomace, which is mainly composed of grape skins, grape seeds and wine mud. Grape pomace is rich in a variety of nutrients, such as protein, carbohydrates, vitamins, minerals, plant fiber and other organic compounds: such as proanthocyanidins, phytosterol, unsaturated fatty acids [1]. The content of grape seed is the main substance among the by-product of wine production. During wine making, 1 kg crushed grape will produce more than 0.2 kg grape residue, and a quarter of the residue is grape seed [2]. So, grape seeds are abundant in grape residue and also easy to isolated from the grape residue. There are a variety of active ingredients (such as proanthocyanidins, resveratrol, catechin, epicatechin, gallic acid, vanillic acid, unsaturated fatty acids) in grape seeds, and which have anti-oxidation, anti-cancer, lowering blood lipids and other effects. These years, the researchers focused on extract the oil from grape seed and made much progress, the oil has been applied in various fields: such as high-grade edible oil, health care products, skin care products, leather maintenance oil and so on. However, relatively fewer work on other ingredients in grape seed has been reported. In China, much amount grape seed was produced during wine producing each year, and this by-product was not fully exploited. In this paper, we mainly reviewed the progress of chemical constituents and biological activities so as to provide reference for the researchers for fully developping and utilizing this resource.

Active Ingredients in Grape Seeds

Polyphenols

Polyphenols extracted from grape seeds are the important secondary metabolites. Grape polyphenols are excellent natural antioxidants, which are widely used in medical, food and daily fields [3-5]. The polyphenols with a content of 70% in grape seed are composed of procyanidins, catechins, resveratrol, etc. Catechin compounds, such as catechin, epicatechin, and epicatechin gallate (Figure 1), are not only the main single dimer in grape seeds, but also the constituent units of oligomer and hyperomer of proanthocyanidins. The content of polyphenols varied among grape varieties [6].

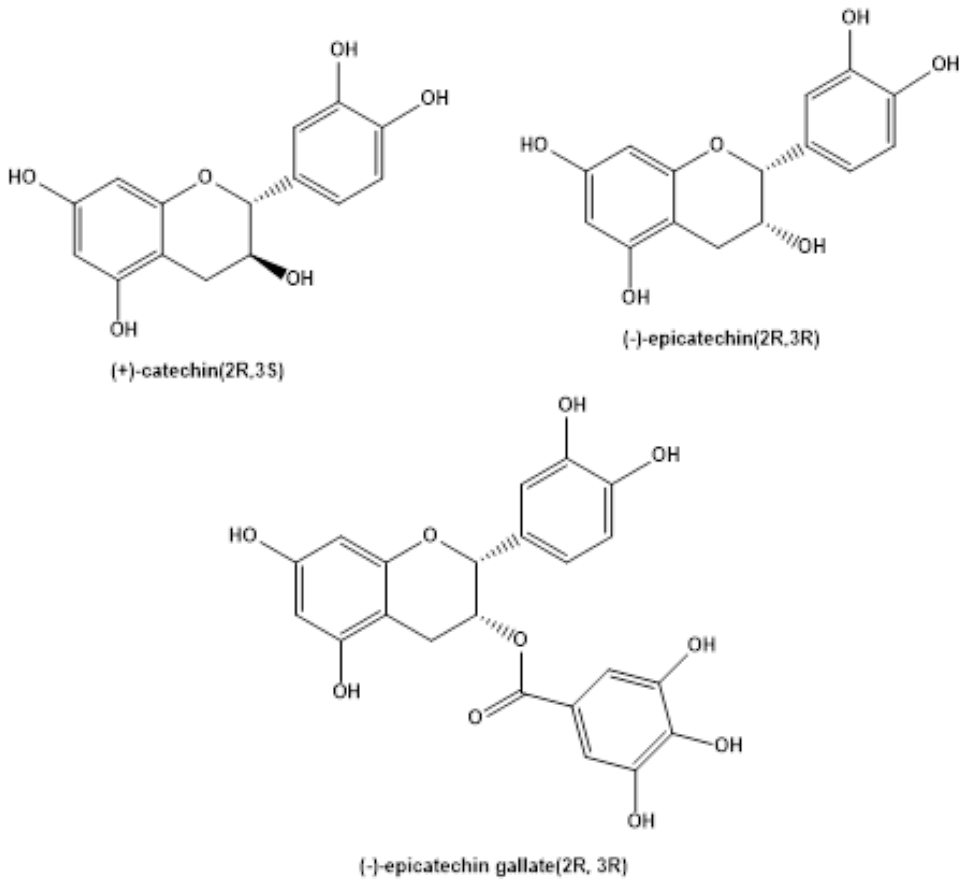

Figure 1: proanthocyanidin monomers structure diagram

Proanthocyanidins

Proanthocyanidins are the most abundant polyphenols in grape seeds. Proanthocyanidins have different structures in different plants [7]. Proanthocyanidins in grape seeds were bonded by C4-C8 (linear) or C4-C6 (branched), and the average degree of polymerization was 2.4-16.7. Catechin dominated the terminal and epicatechin dominated the intermediate extension chain. Procyanidins from dimer to pentamer are referred to as oligomers, and procyanidins in excess of pentamer are referred to as hyperpolymers [8]. Researchers have isolated and identified 29 proanthocyanidins from grape seeds: including 3 proanthocyanidins monomers; 14 dimers (6 of which are gallate forms); 11 trimers and 1 tetramer [9]. Procyanidins have different degrees of polymerization, chemistry, biological activity and application value. Many studies about the procyanidins have been carried out because of the high biological activity of the dimer. The structural forms of the isolated and identified dimers are listed below (Figure 2), which were named as proanthocyanidins B1-B8 respectively. Procyanidins B1-B4 is connected by C4-C8 bond with a high content in grape seeds, while procyanidins B5-B8 is linked by C4-C6 bond with a less content [8]. It was also found that proanthocyanidin monomers, dimers and trimers isolated from grape seeds had the ability to capture free radicals and showed anti-oxidation [10]. The antioxidant efficacy of proanthocyanidins is 20 times higher than that of vitamin E and 50 times higher than that of vitamin C [11]. In addition, proanthocyanidins also have anti-cancer, improve immune ability, improve intestinal environment, prevent heavy metal poisoning and other functions [12, 13]. It also reported that the composition and content of phenolic compounds in extracts are related to extraction solvents [14, 15]. Cui et al. found that eutectic solvent combined with ultrasonic-assisted extraction of phenolic substances in Cabernet Sauvignon grape seeds was significantly superior to traditional organic extraction solvent [16]. The total phenol content of choline chloride-lactic acid extract was the highest (2505.13mgGAE/100 g).

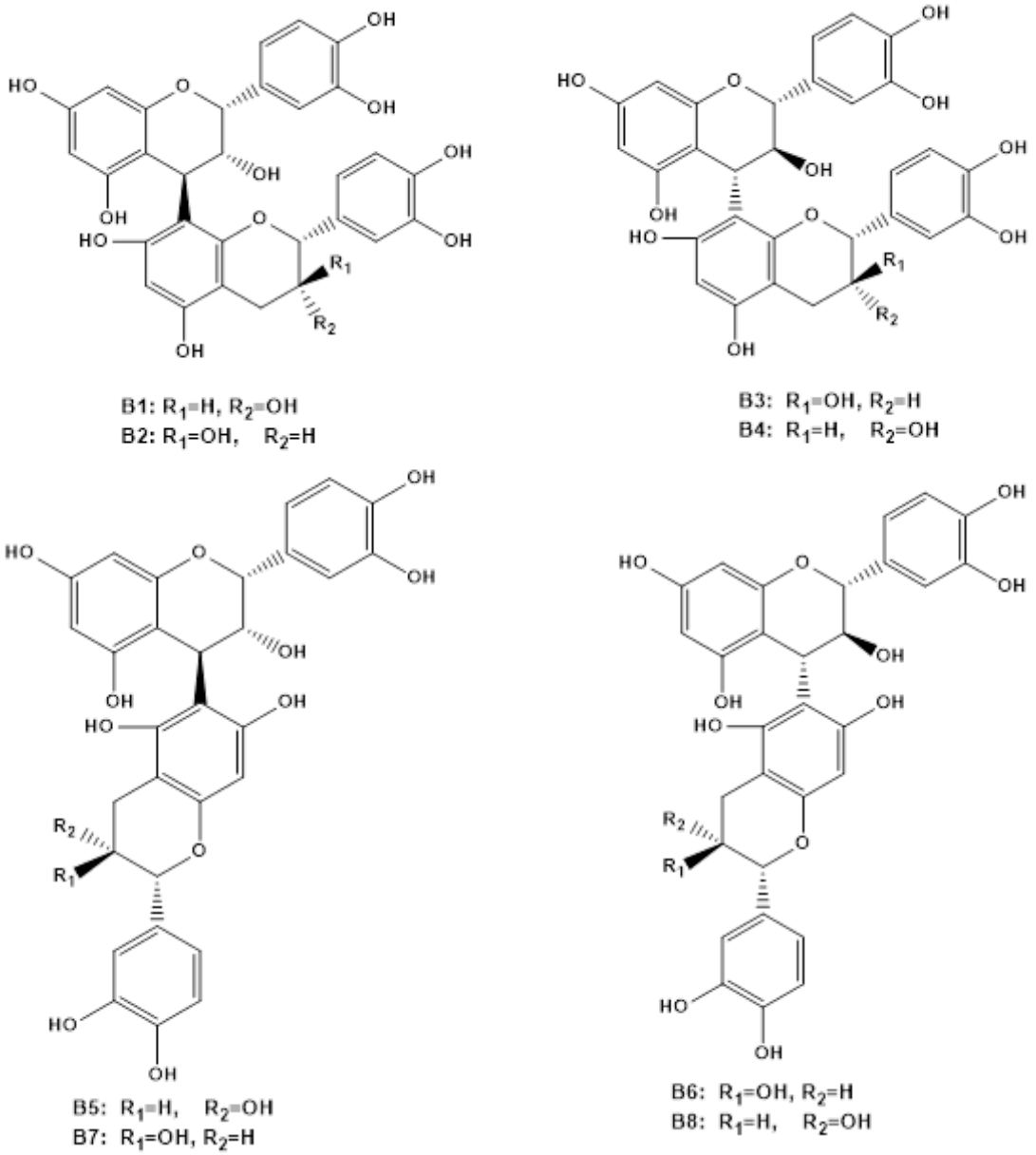

Figure 2: proanthocyanidin dimers structure diagram

Resveratrol

Resveratrol is a kind of natural polyphenolic substance with potent biological activity in the subclass of stilbene [17]. The natural resveratrol has two kinds of structures, cis-conformation and trans-conformation, and which mainly exists in the trans-conformation [18]. It has been found that resveratrol has anti-inflammatory, anti-depressant, anti-cancer, prevention and treatment of cardiovascular diseases and other pharmacological activities [19-24]. The variety and position of grape have great influence on the content of resveratrol. The content of resveratrol in grape of general wine variety is higher than that of fresh grape variety [25]. You et al. adopted microwave-assisted extraction of resveratrol and optimized the extraction process [26]. The yield of resveratrol was 3.96 mg /g.

Catechins

Because tea polyphenols are mainly catechins, the study of catechins is mainly concentrated in tea. Catechin has anti-inflammatory, antibacterial, antiviral and antioxidant effects [27-30].

Phytosterol

Phytosterols are natural compounds found in vegetable oils, nuts and other foods. Phytosterols mainly include sitosterol, rapeseed sterol, stigmasterol, and rapeseed sterol, etc. (Figure 3), which are similar to cholesterol in structure [31]. It has many physiological functions, such as cholesterol reduction, anti-oxidation, anti-inflammation, immune regulation and so on. It has many physiological functions, such as cholesterol reduction, anti-oxidation, anti-inflammation, immune regulation and so on [32-35]. There are about 13 kinds of grapeseed oleosterols with total amount ranging from 222.5 to 234.9 mg /100 g. The proportion of phytosterol components was relatively fixed, β-sitosterol accounted for 67.11%-71.90% of total phytosterol, campesterol 9.6%-10.5% of total phytosterol, stigmasterol 8.16%-10.8% of

total phytosterol [36-39]. Because the human body cannot synthesize phytosterol, it can only be absorbed from food, and the absorption of rapeseed sterol and β-sitosterol is the best in the human body. Nowadays, the research on phytosterols in oils and fats is mostly focused on soybean oil, rapeseed oil and so on [39, 40]. The rich variety of phytosterols in grape seeds has good development potential.

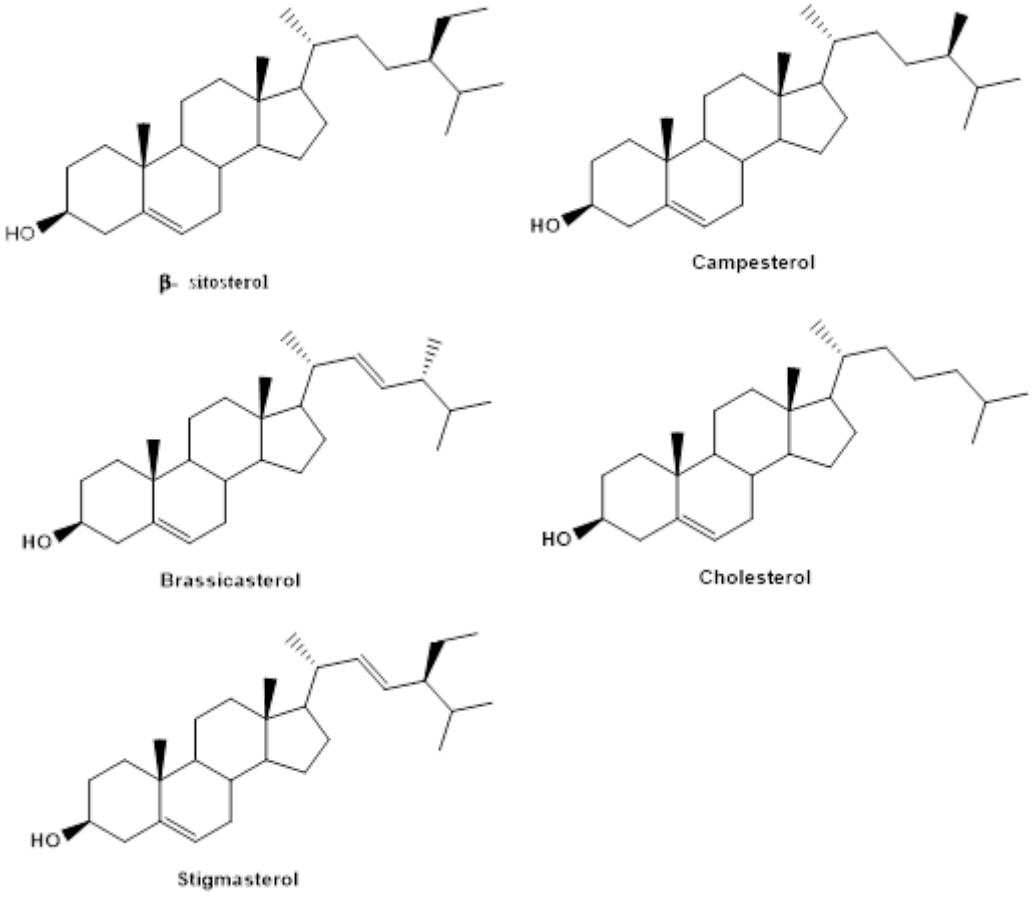

Figure 3: β-sitosterol, campesterol, stigmasterol, brassicasterol, cholesterol structure diagram

Vitamin E

Grape seeds contain vitamins A, D, E and other vitamins, and vitamin E is the most abundant [41]. Vitamin E is a kind of natural fat-soluble antioxidants in grape seeds, which has many functions such as antioxidation, anticancer, prevention of cardiovascular disease, regulation of immune function and so on [42-45]. Vitamin E is composed of tocopherol and tocoptrienol, consisting of eight compounds, which are α-, β-, γ-, δ -tocopherol and corresponding tocotrienol. α-tocopherol is generally recognized as the most active form of vitamin E [46].

Vitamin E is mainly in the form of tocopherol in common vegetable oils, and the content of tocopherol is higher in palm oil, grape seed oil and rice oil [46]. IlknurDemirtas et al studied seven grape varieties in Turkey and found that the vitamin E was dominated by α -tocopherol (77.33-225.40 mg/kg), α-tocotrienol (137.19 -264.33 mg/kg) and γ-tocotrienol (74.79-322.18 mg/kg) [47]. MinjungWie et al. studied 14 grape varieties in Korea, and found that the total content of vitamin E was 4.8~9.9mg/100g [48]. The highest content of γ-tocotrienol was 1.6~5.5mg/100g, followed by α-tocopherol, α- tocotrienol and γ-tocopherol. The contents of tocopherol and tocopherol of vitamin E in grape seeds are relatively balanced and have good development potential.

Unsaturated Fatty Acids

The unsaturated fatty acids in grape seed oil accounted for 90% of the total oil content. The main component is linoleic acid (linoleic acid, (9Z,12Z)-9,12-Octadecadienoic acid), with a content of more than 70%. Linoleic acid is an important essential fatty acid, which cannot be synthesized by human body. Linoleic acid can reduce the contents of cholesterol, glycerol, low density lipoprotein and very low-density lipoprotein in human blood. Linoleic acid has the functions of preventing atherosclerosis and maintaining the balance of blood lipid metabolism. It is called "vascular scavenger". Except for linolenic acid, unsaturated fatty acids in grape seed oil also contain oleic acid (the content is about 15%), and other fatty acids with nutritional value: such as palmitic acid, stearic acid [49, 50].

Protein

Grape seeds contain about 11% protein. Xu Shenhong et al. found that there were 16 kinds of amino acids in grape seeds by acid hydrolysis, including 7 essential amino acids (Table 1) [51]. The protein content in the residue of grape seed (after oil extraction) is about 13%, in which the contents of valine, methionine, arginine and phenylalanine are similar to those of soybean protein, which is a new high quality protein resource. Grape seed protein also

contains highly safe bioactive peptides, which not only provide nutrients for growth and development, but also have physiological functions: such as disease treatment, disease prevention and regulation of human physiological functions [52].

Table 1: Amino acid content of grape seeds (mg/100mg)

Amino acids	content	Amino acids	content
Aspartic acid	0.63	isoleucine	0.36
threonine	0.26	leucine	0.60
serine	0.40	tyrosine	0.17
glutamate	2.20	phenylalanine	0.34
glycine	0.84	lysine	0.18
alanine	0.42	histidine	0.20
cystine	0.00	arginine	0.53
valine	0.51	proline	0.11
methionine	0.01		

Mineral Substances

Grape seeds contain 3% minerals. Major elements and trace elements are abundant. Among the major elements, the contents of K, Ca and P are higher, while the content of Na is low. Among the trace elements, the contents of Fe, Mn, Cu, Zn and other nutrient elements are relatively high, especially the content of Fe element is almost the same as that of major elements, while Pd, Cd and other heavy metals are not detected (Table 2) [51].

Table 2: Mineral element content of grape seed

elements	Contents(mg/g)	elements	Contents(mg/kg)
K	2.769	Cu	8.526
Ca	2.414	Zn	8.126
P	2.199	Li	4.480
Mg	0.878	Al	13.290
Na	0.200	Si	4.771
Fe	0.293	Sr	5.581
Mn	0.033	Pd	not detected
		Cd	not detected

Other Active Ingredients

Grape seeds also contain plant fiber, chlorophyll, carotenoids and other active components, which improve the nutritional value of grape seeds [49, 53].

Biological Activities

Anti-Oxidation and Anti-Aging

In recent years, with the gradual attention to food safety, the development and utilization of antioxidants are attracting people's attention. Antioxidants are divided into synthetic antioxidants and natural antioxidants. However, some synthetic antioxidants pose a potential threat to human health. Therefore, it is a trend to look for safer, natural and efficient antioxidants from the natural edible plant resources. Grape seeds have become a kind of natural antioxidant resource, due to it contains abundant antioxidant ingredients: such as polyphenols, phytosterols and vitamin E.

With the deep research, it was found that the grape seed polyphenols had strong antioxidant efficacy, and the antioxidant efficacy was positively correlated with the concentration of grape seed polyphenols [54]. Grape seed polyphenols can reduce the formation of lipid peroxidation products in myocardium, biofilm, serum and other tissues of mice induced by adriamycin, enhance the activity of SOD, GSH-Px and other antioxidant enzymes, and protect the ATPase activity of mitochondria.

It suggested that the aging can be defined as a complex physiological process in which tissues and organs gradually lose their ability to resist injury and repair, which eventually leads to the apoptosis of living organisms. Under the action of the environment, the aging and other factors, the oxidation and antioxidant balance in the body is destroyed, and then produce free radicals. When the concentration of free radicals reaches a certain "threshold", the free radical chain reaction causes denaturation and cross-linking of macromolecules in the body, which damages the structures of tissues and organs, and leads to oxidative stress injury of the organism, and finally leads to aging and death [55, 56]. Natural antioxidants can prevent and cure tissue lesions and delay aging by scavenging excessive free radicals in the body [57]. The natural active substances in grape seeds can delay aging by scavenging free radicals and promoting metabolism.

When Wang Chuanxian et al. studied the antioxidant efficacy and free radical scavenging effect of grape seed polyphenols, they found that grape seed polyphenols had scavenging effect on

•OH, O2-, LOO•, and showed an obvious dose-effect relationship [58]. Guo et al. the ability of proanthocyanidins to scavenge superoxide anions and hydroxyl radicals in vitro was determined by chemiluminescence and cytochrome reduction methods, and compared with vitamin C, vitamin E, SOD and catalase [59]. It was found that the ability of proanthocyanidins to scavenge superoxide anions and hydroxyl radicals was 84% and 98% resectively, and higher than that of vitamin C.

Anticancer Activities

According to the World Health Organization's International Agency for Research on Cancer (IARC), there will be about 19.29 million (10.06 million in men and 9.23 million in women) new cases of cancer in 2020. Cancer is still an insurmountable problem in the world today. There are many kinds of anticancer active substances in grape seeds-grape seed polyphenols, phytosterols, vitamin E and so on. Li Xiaomin et al. found that the concentration of proanthocyanidins increased, the activity and cell cloning of human skin squamous cell carcinoma (A431 cells) decreased gradually, and the cell apoptosis also increased gradually [60]. Grape seed polyphenols can induce A431 cell apoptosis and inhibit A431 cell proliferation, which may be related to the inhibition of p-PI3K, p-Akt and p-GSK-3 β pathway expression. Wang et al. found that autophagy occurred in human hepatoma cells (HepG2) treated with grape seed polyphenols [61]. Further studies showed that the grape seed polyphenols could induce phosphorylation of p-JNK, p-ERK and p-p38MAPK related to MAPK pathway and reduce the expression of survivin. And grape seed polyphenols may lead to programmed death cascade transformation of apoptosis and autophagy. ManiSuganya et al. studied the effect of the grape seed polyphenols on human colon cancer cells (HT-29), the reslults showed that the grape seed polyphenols promoted apoptosis of HT-29 cells through chromatin condensation and cell membrane blistering, and the reproductive cycle of HT-29 cells was blocked in G2/M phase [62]. Studies have also shown that a regular diet rich in phytosterols can reduce the risk of cancer by 20 percent, and phytosterols can also achieve the combined anti-tumor response by improving the immune response recognition of cancer, affecting hormone-dependent endocrine tumor growth and sterol biosynthesis regulation [63]. Vitamin E controls the growth, proliferation, differentiation and apoptosis of cancer cells by regulating the MAPK pathway [43]. High concentration of resveratrol inhibited the growth of triple negative breast cancer cells through MAPK signaling pathway and induced autophagy and apoptosis [20]. Xu et al. studied the preventive effect of curcumin and catechin alone and in combination on colon cancer induced by 1,2-dimethylhydrazine in rats [64].

Anti-Inflammatory

Grape seed has anti-inflammatory activity, which is closely related to its polyphenols, phytosterols, unsaturated fatty acids and vitamin E. Unsaturated fatty acids can play an anti-inflammatory role by inhibiting the transcription factors NF-KB and C-Jun amino-terminal kinase signaling pathways in adipocytes, and can also reduce the expression of pro-inflammatory factor genes in liver and adipose tissue [65]. Vitamin E and polyphenols in grape seeds can also inhibit the production of inflammatory factors and improve insulin sensitivity in mice by inhibiting JNK pathway and serine phosphorylation of IRS1[66]. Chen Zehua et al. found that grape seed oil may reduce inflammatory response by regulating the expression levels of cytokines IL-1 and IL-2, thus improving hypothyroidism [67]. H.Harbeoui et al. found that grape seed proanthocyanidins inhibit the production of proinflammatory cytokines in RAW 264.7 cells by inhibiting the activation of MAPKs and NF- κ B signal pathways [68]. Liu et al. found that grape seed proanthocyanidins alleviate inflammation in mice with pulmonary hypertension by reducing the expression of PPAR- γ/COX-2 [69]. Valerio et al. have shown that β-sitosterol can increase the activity of anti-inflammatory factors and decrease the activity of pro-inflammatory factors by inducing lipopolysaccharide to secrete macrophages [70]. At the same time, NF- κ B and STAT1 signal pathways were inhibited to achieve anti-inflammatory effect.

Reduce Blood Fat and Protect Cardiovascular System

The effect of grape seed on reducing blood lipid is related to the high content of linoleic acid and phytosterol in grape seed polyphenols, grape seed oil. Yang Xiaojun et al. found that proanthocyanidins, resveratrol and grape seed oil extract could effectively reduce serum total cholesterol, serum triacylglycerol and Low density lipoprotein cholesterol in mice [71]. Tamami Odai et al. found that different doses of grape seed proanthocyanidins can maintain vascular elasticity and normal blood pressure [72]. In a 15-day trial, phytosterols reduced low density lipoprotein and increased high density liptein levels in dogs with no side effects [73].

Curb Obesity

Obesity is affected by genetic and environmental factors. With the improvement of living standards, more and more complex environmental factors lead to obesity and obesity-related diseases.

The unsaturated fatty acids and tocopherol in grape seeds are closely related to the functional activity of inhibiting obesity. Unsaturated fatty acids can reduce fat accumulation in the body by stimulating lipid peroxidation in liver tissues, inhibiting fat generation in liver tissues, and promoting fatty acid oxidation in muscles. Grape seed oil and tocopherol in grape seed oil acted on human adipose stem cells respectively. Grape seed oil could significantly reduce the aggregation of human adipose stem cells, which was better than rice bran oil and olive oil. Tocopherol in grape seed oil can reduce mRNA and protein expression related to fat production [74]. Linoleic acid and phytosterols, whether used alone or in combination, can reduce adipose tissue in mice [75].

Other Biological Activities

Grape seed proanthocyanidin extract can improve the damage of ionizing radiation to hematopoietic progenitor cells by regulating the antioxidant genes of fokhead box transcription factor O1, so as to achieve the anti-radiation effect [76]. In addition, grape seed has a neuroprotective effect on retinal tissue, and has the function of protecting testicular tissue structure, inhibiting spermatogenic cell apoptosis and other functions [77, 78].

Conclusions and Future Prospects

With the development of the wine industry, the wine industry chain will inevitably produce a large number of by-products-grape seeds. Although grape seeds are now discovered and used to make health products, cosmetics and daily necessities, a large part of them are still used as feed, fertilizer or even directly discarded, which increases the environmental pollution to a certain extent. How to maximize the utilization of the discarded grape seeds and realize the best use of this materials? The research on grape seeds has never stopped since the first extraction of proanthocyanidins in the 1970s. More and more active components and bioactive functions are being explored and utilized. However, researches on grape seed active ingredients and biological activities mainly focus on grape seed polyphenols for the higher content, while other grape seed active ingredients and biological functions are relatively fewer. Grape seed is a kind of edible natural substance, and which is easily available with large quantity. More and more researchers should focus on studying this natural resource to explore the value of grape seed.

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